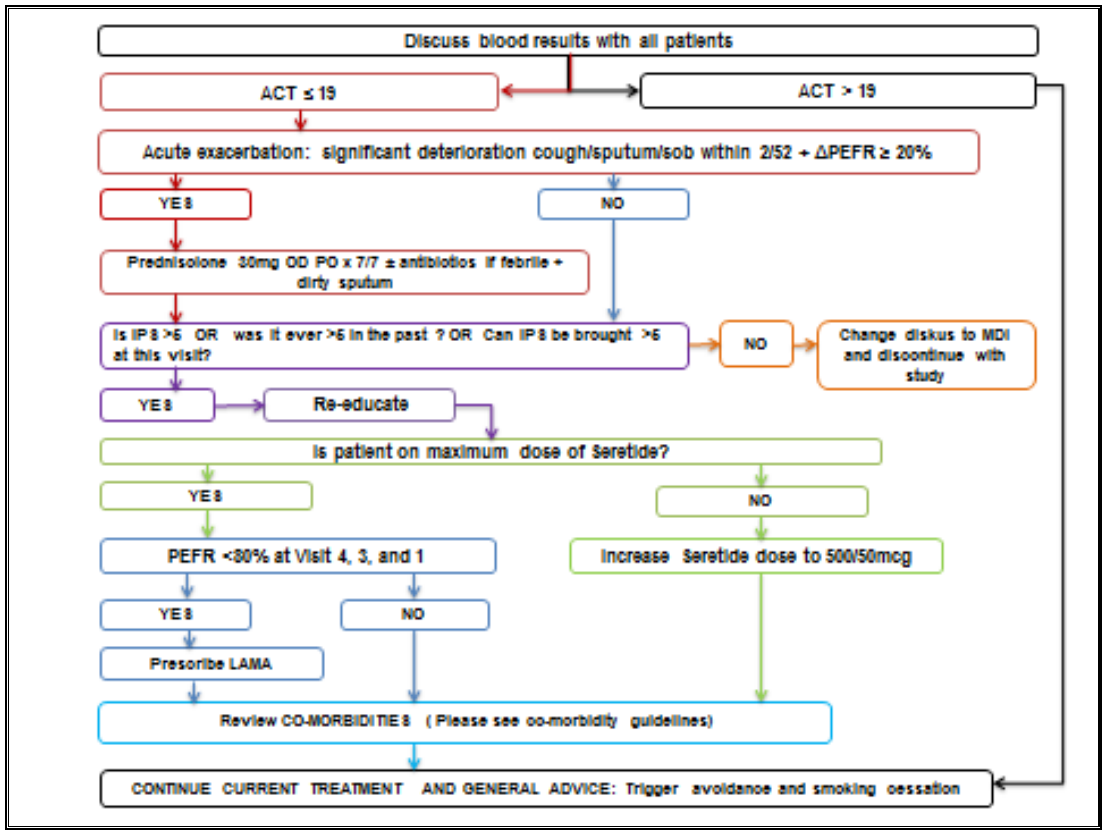
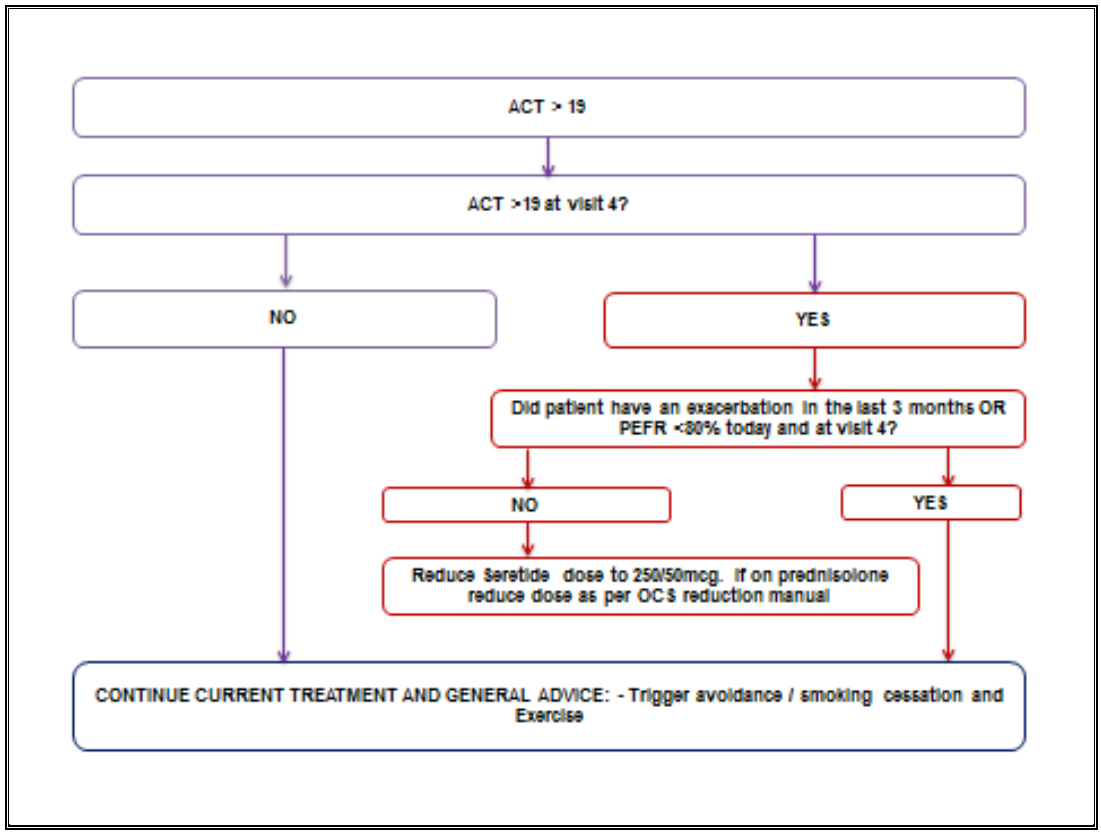
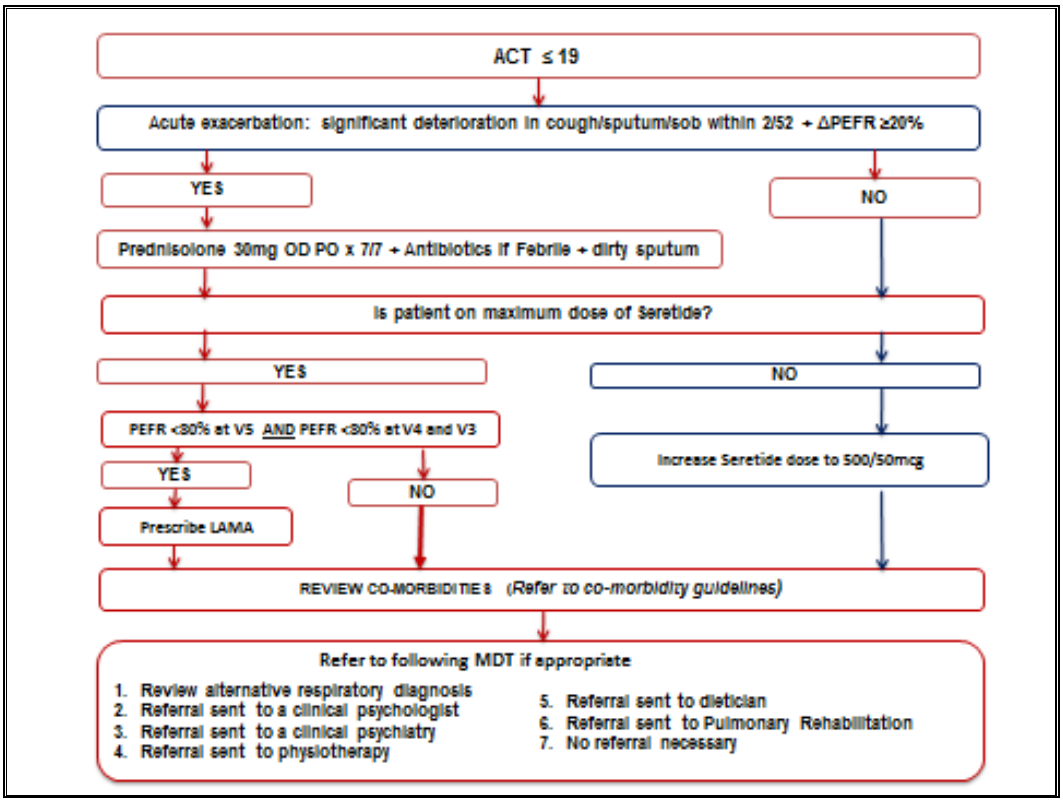
*Appendix 1: Physician script at visit 4 for control group*



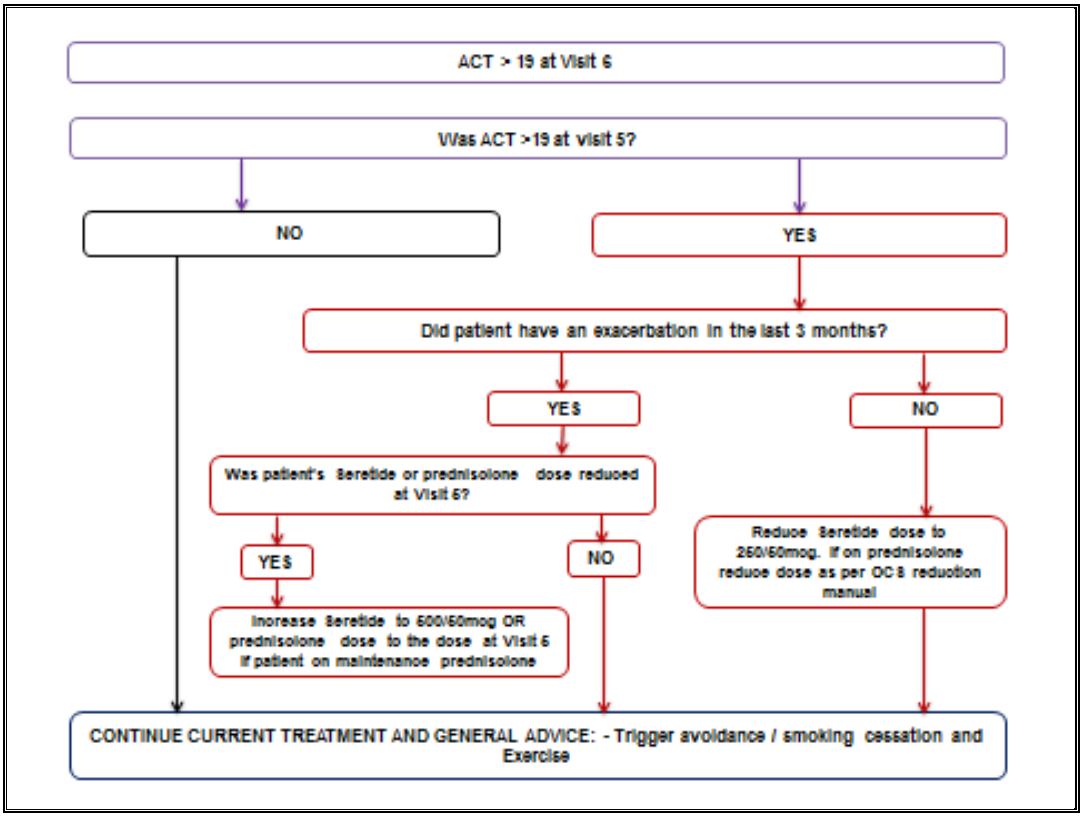
*Appendix 2a: Physician script at visit 5 for the control group (ACT >19)*



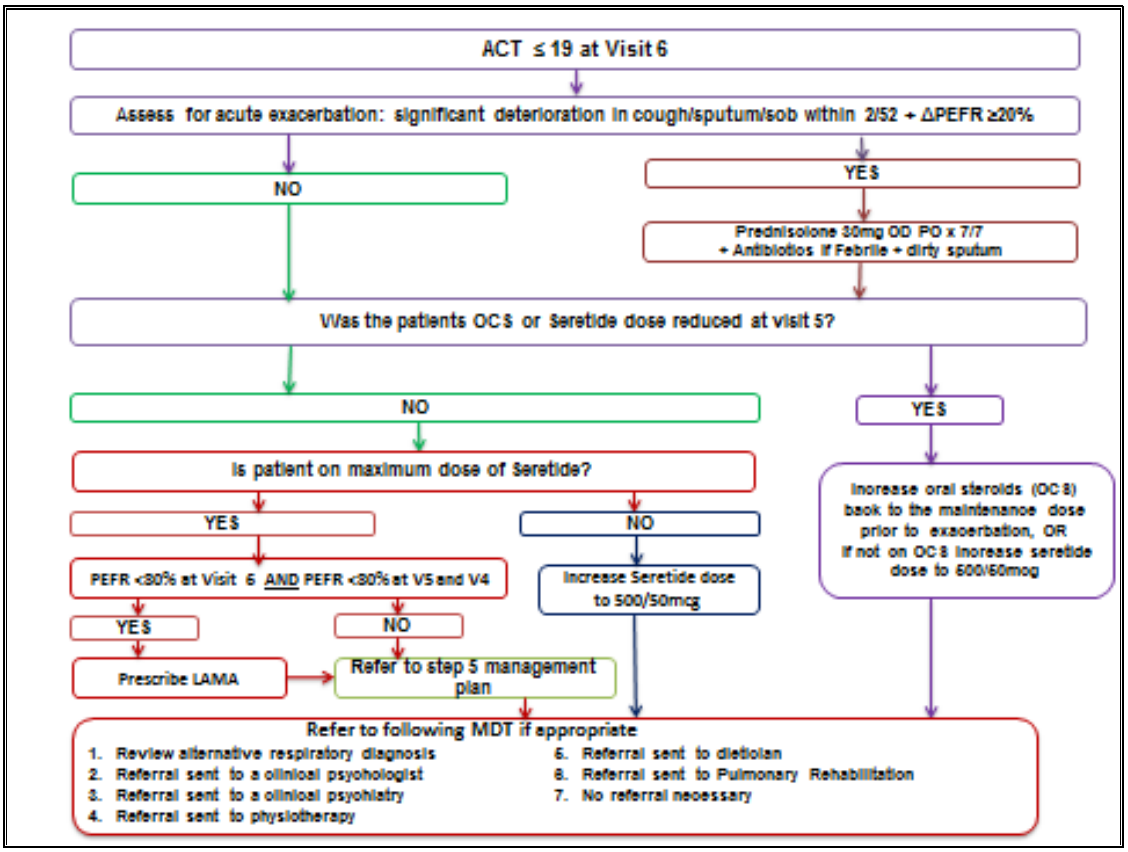
*Appendix 2b: Physician script at visit 5 for the control group (ACT ≤19)*



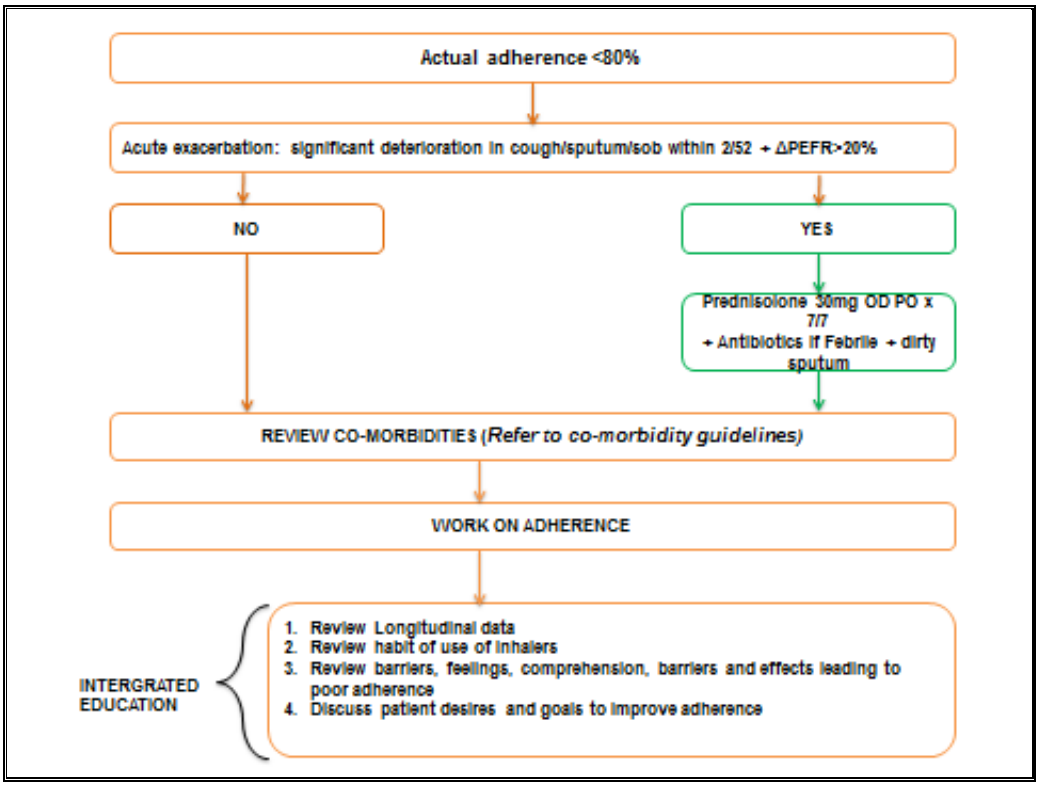

*Appendix 3a: Physician script at visit 6 for the control group (ACT >19)*



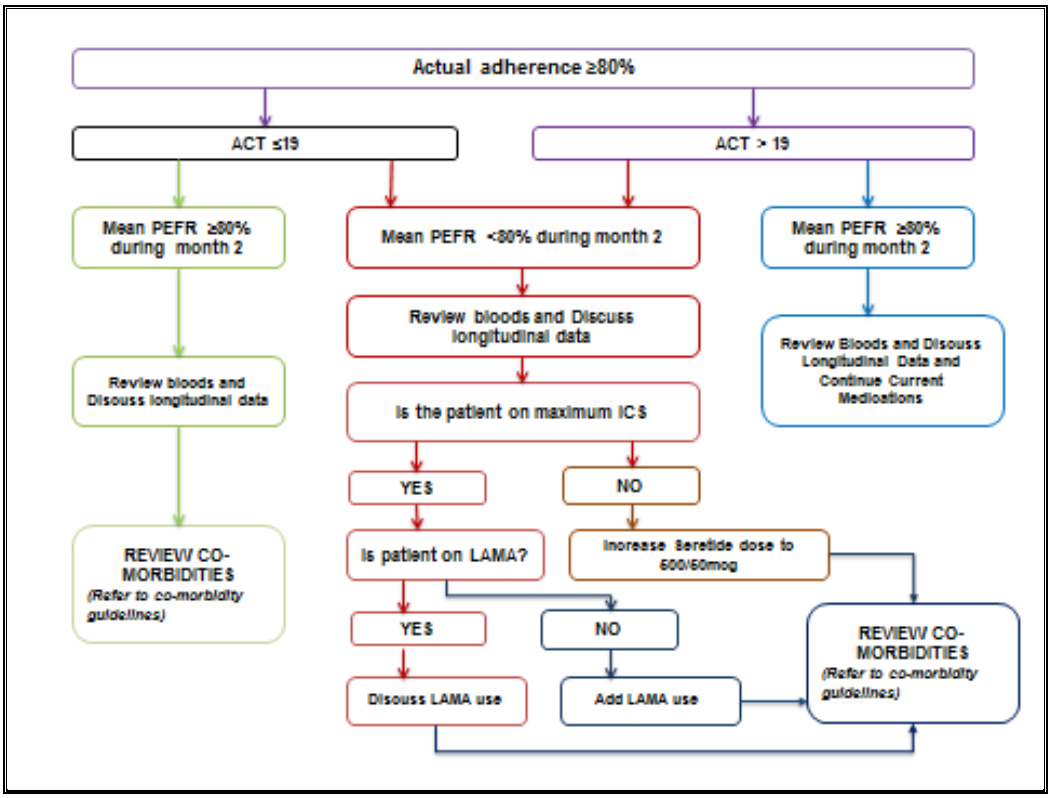
*Appendix 3b: Physician script at visit 6 for the control group (ACT ≤19)*



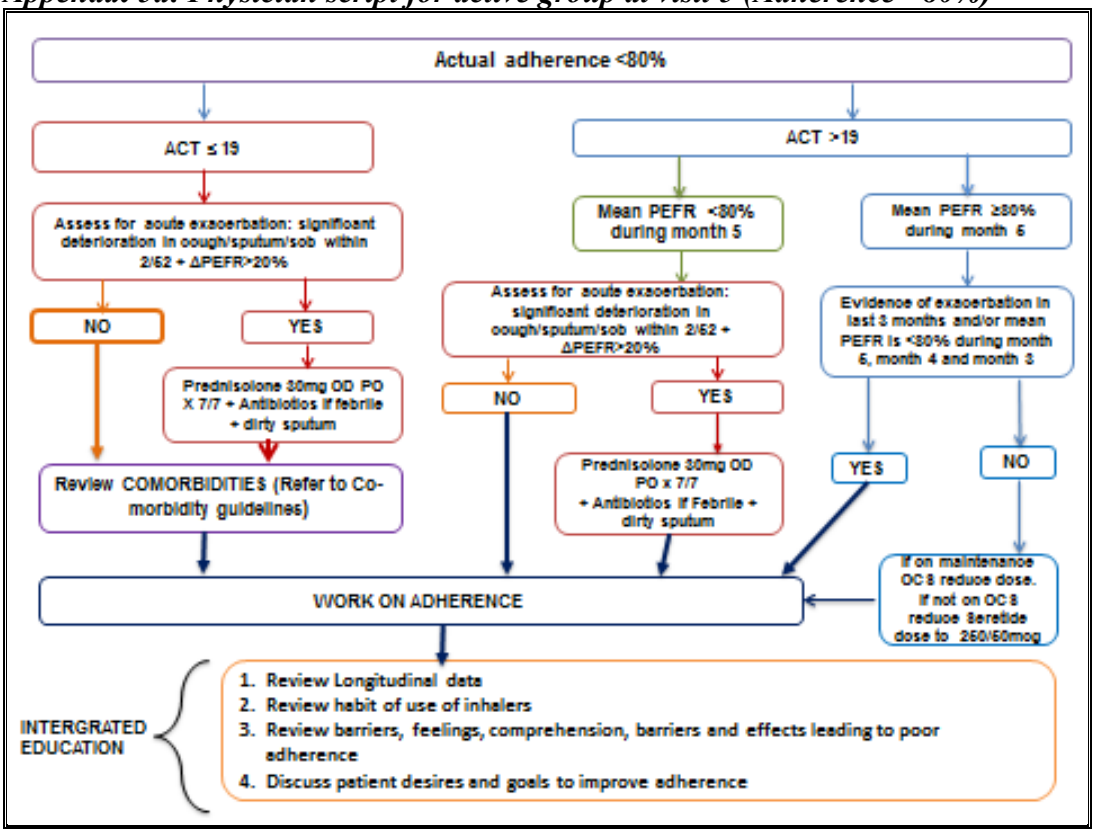
*Appendix 4a: Physician script for Active group at visit 4 (Adherence <80%)*



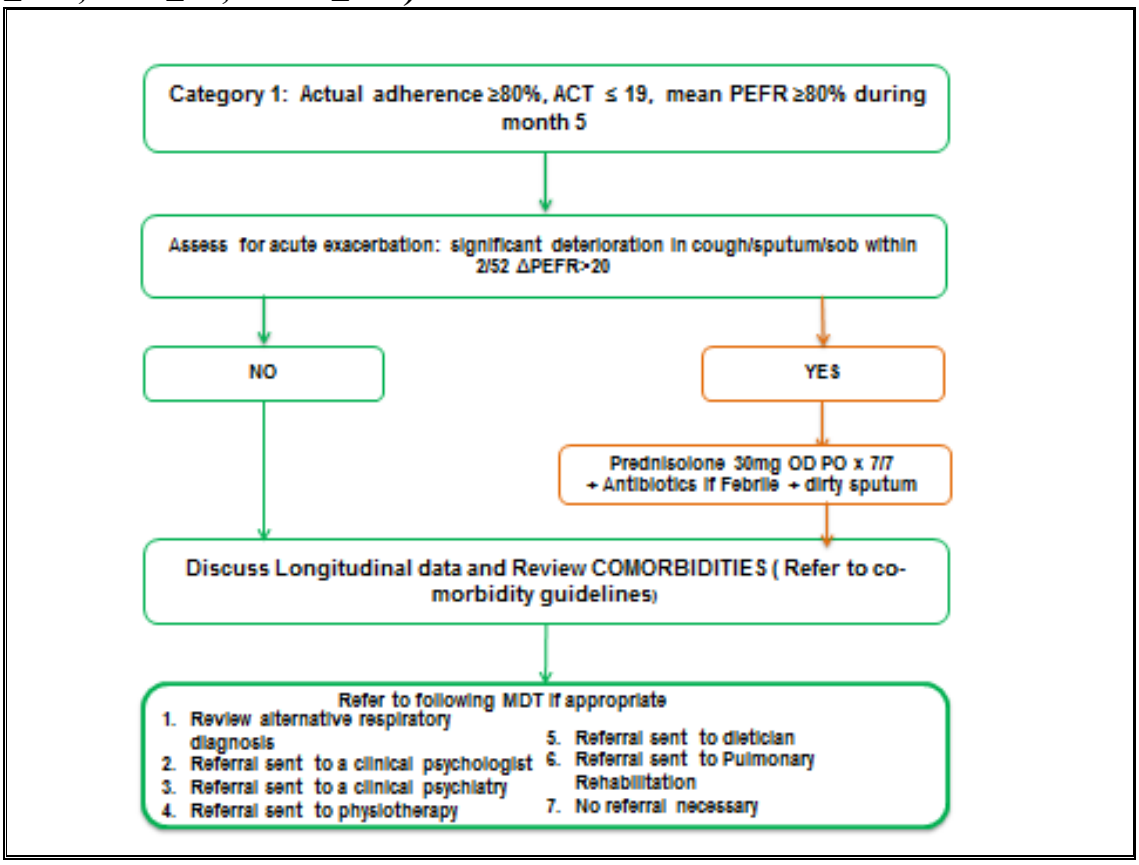

*Appendix 4b: Physician script for active group at visit 4 (Adherence ≥80%)*



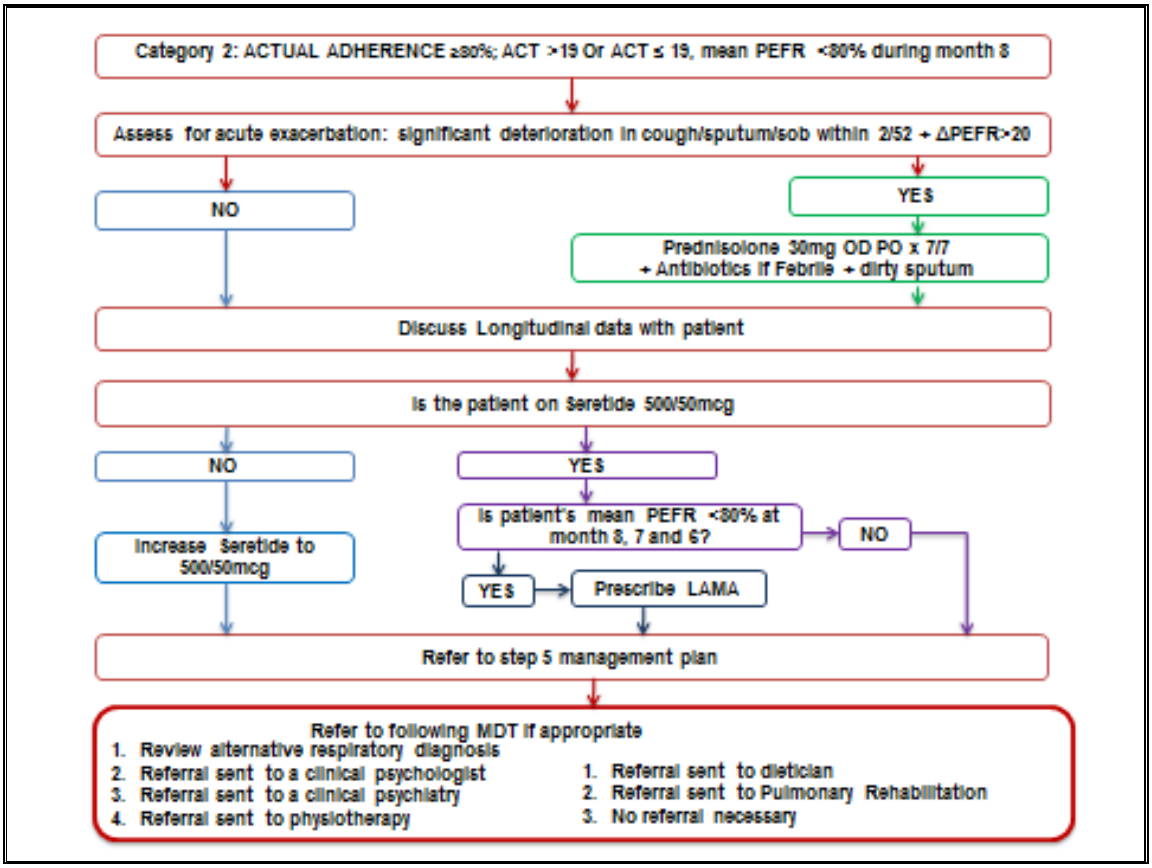
*Appendix 5a: Physician script for active group at visit 5 (Adherence <80%)*



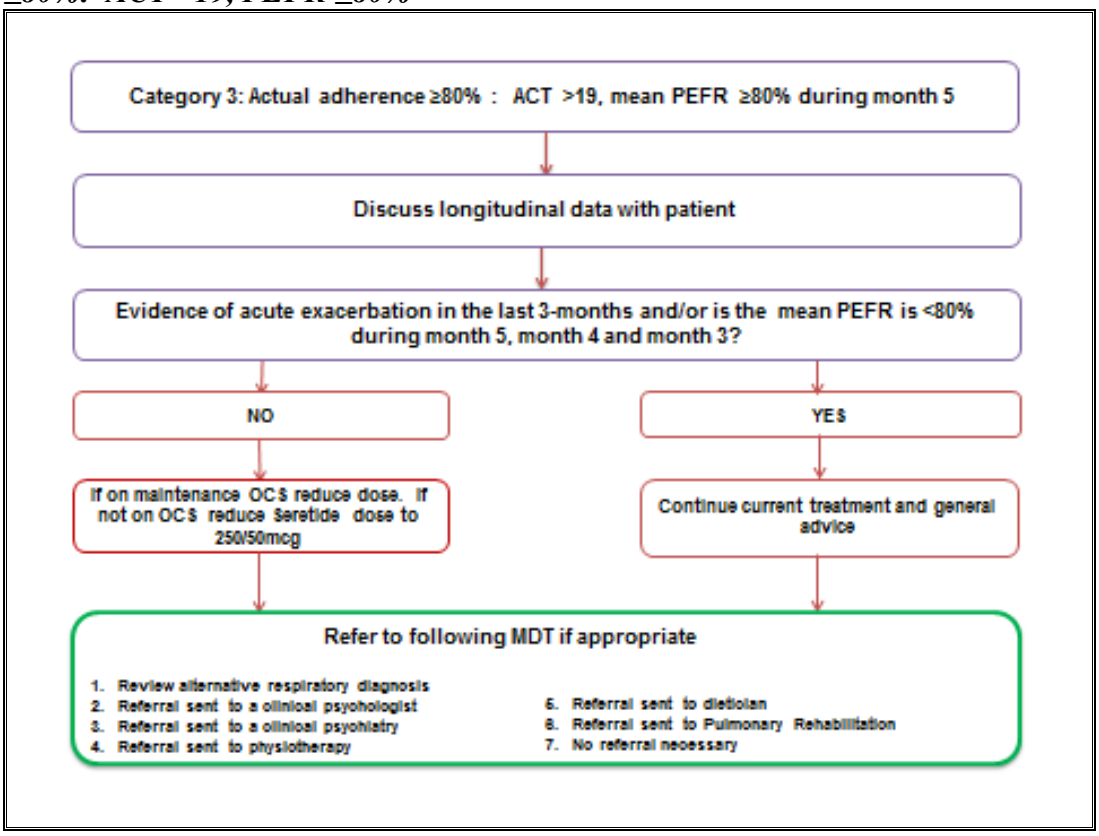

*Appendix 5b: Physician script for active group at visit 5 (Category 1: Actual adherence ≥80%, ACT ≤ 19, PEFR ≥80%)*



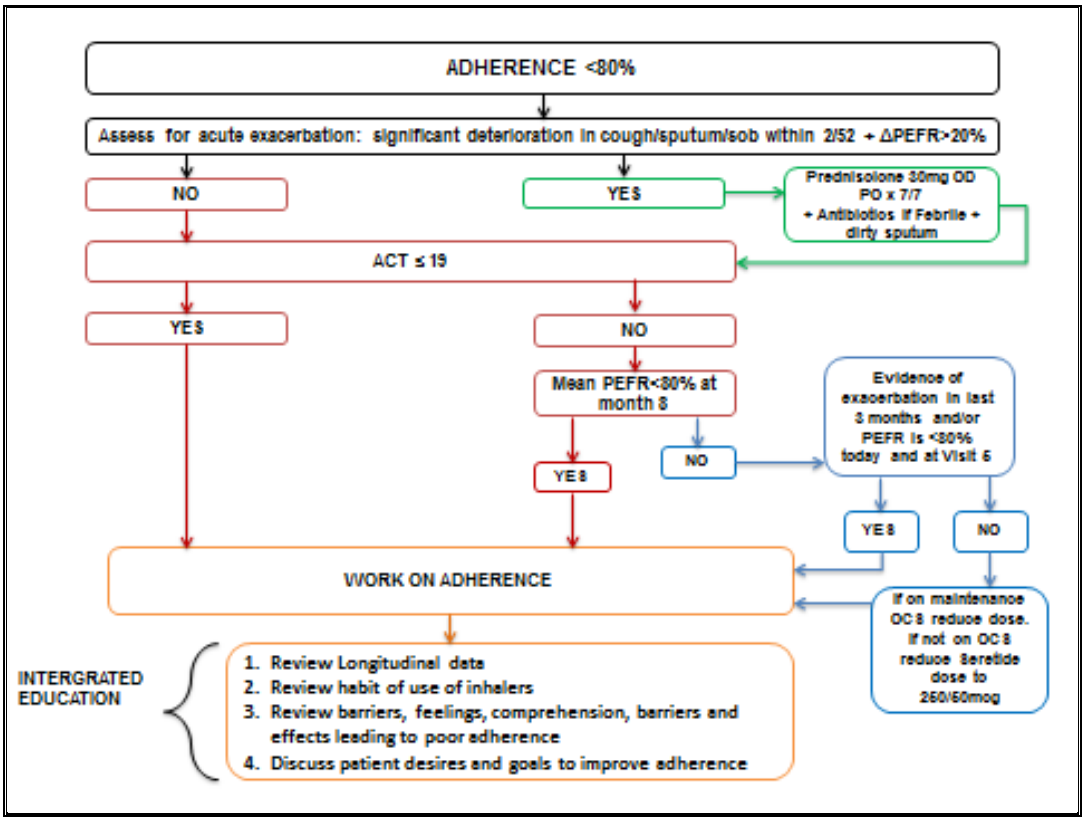
***Appendix 5c: Physician script for active group at visit 5 (Category 2: Actual adherence ≥80%: ACT >19 Or ACT ≤ 19 PEFR<80%)***



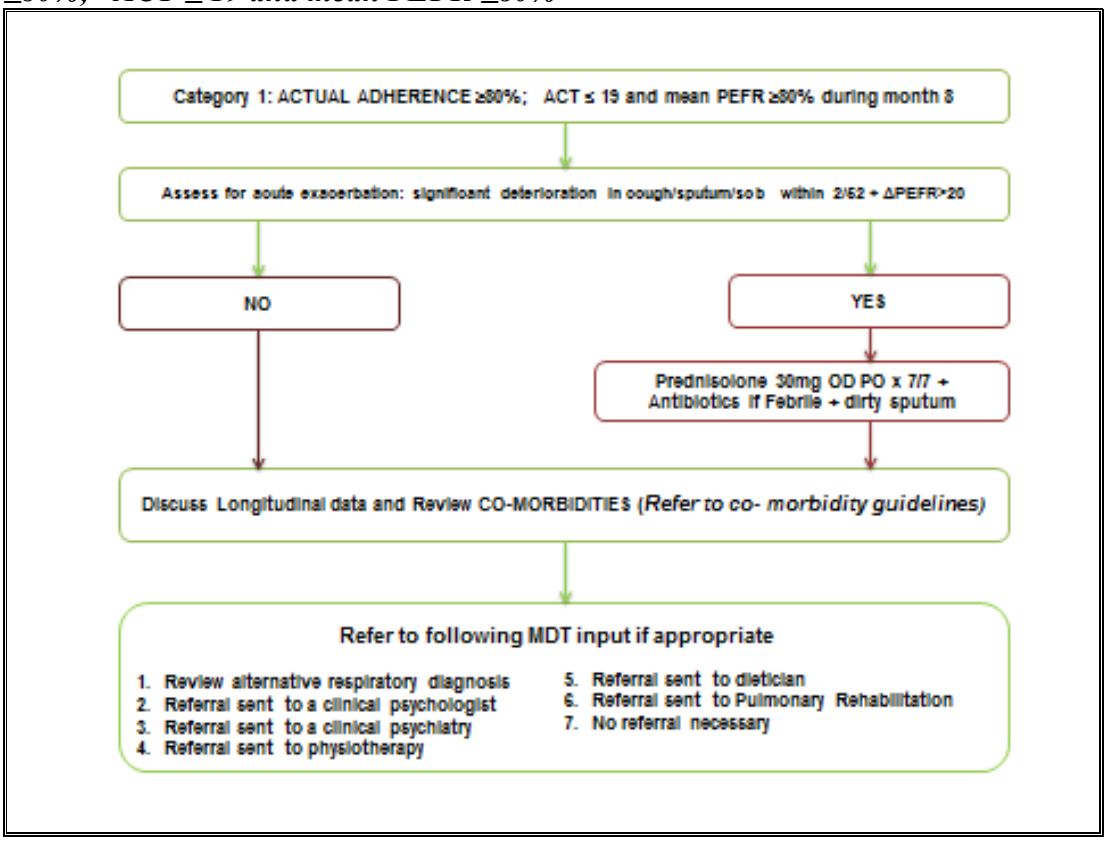
***Appendix 5d: Physician script for active group at visit 5 (Category 3: Actual adherence ≥80%: ACT >19, PEFR ≥80%***



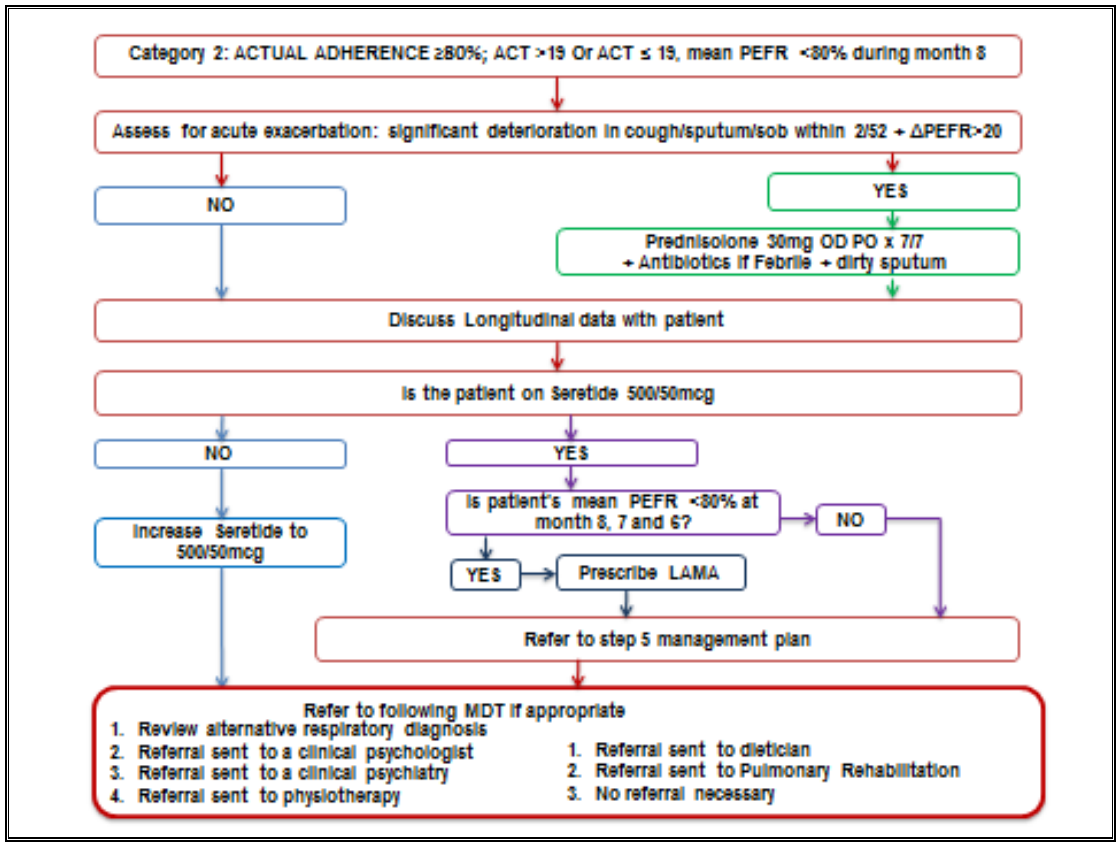
*Appendix 6a: Physician script for active group at visit 6 Actual adherence <80%*



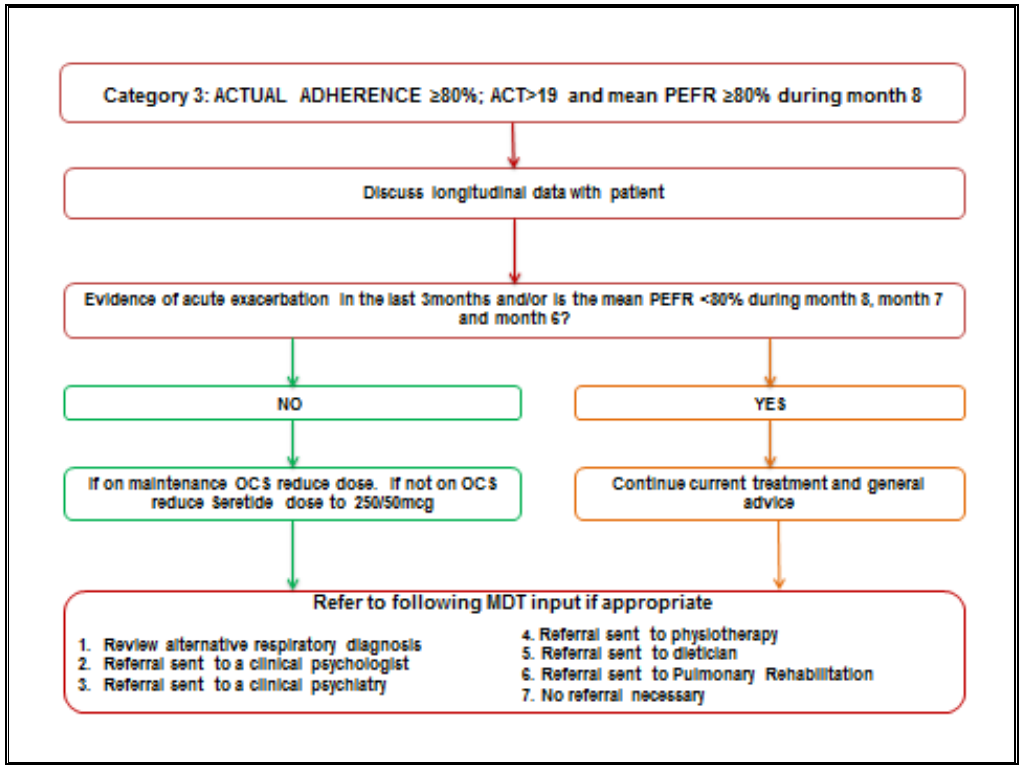

*Appendix 6b: Physician script for active group at visit 6 (Category 1: Actual adherence ≥80%; ACT ≤ 19 and mean PEFR ≥80%*



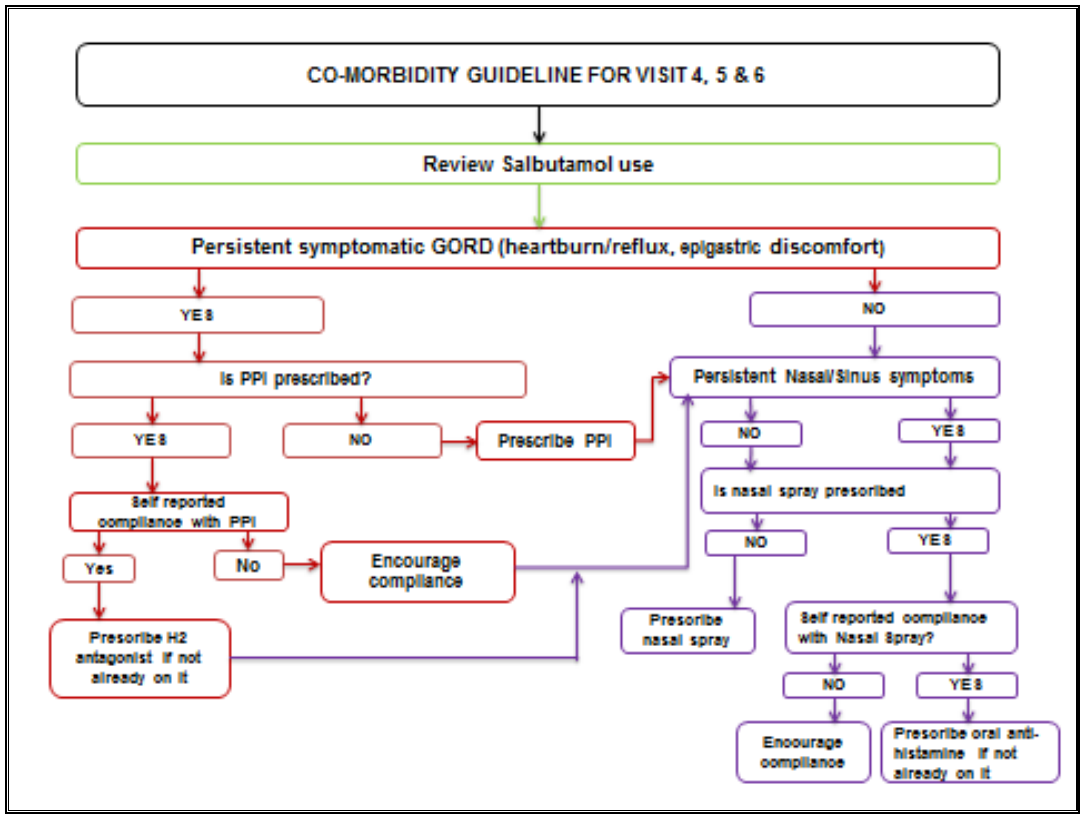
***Appendix 6c: Physician script for active group at visit 6 (Category 2: Actual adherence ≥80%; ACT >19 Or ACT ≤ 19, mean PEFR <80%)***



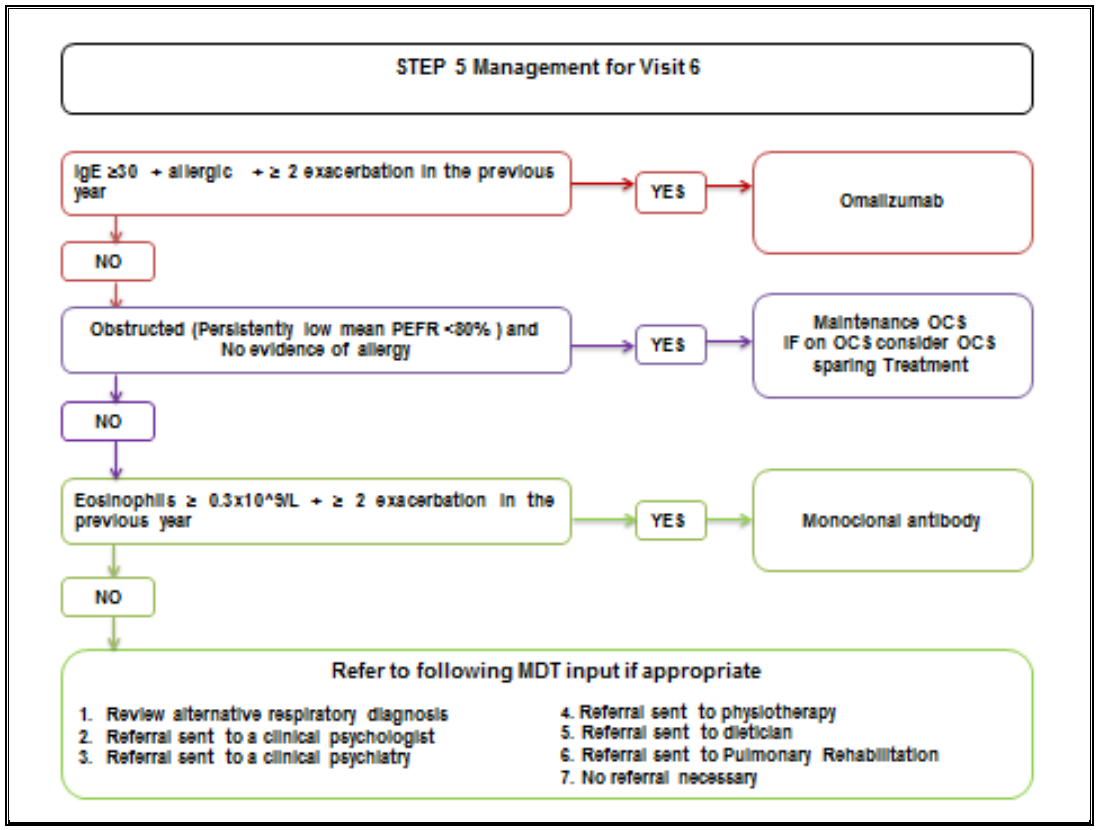

***Appendix 6d: Physician script for active group at visit 6 (Category 3: Actual adherence ≥80%; ACT >19 and mean PEFR ≥80%)***



*Appendix 7: CO-MORBIDITY GUIDELINE FOR VISIT 4, 5 & 6*




*Appendix 8: STEP 5 Management for Visit 6*



## Appendix 9

**Inhaler Proficiency Schedule (IPS)**

**Patient ID: _____**

**Date: _____**

**Visit No: _____**

| | | YES | NO |
|---|---|---|---|
| | **Does the patient hold the outer casing of the inhaler in one hand, whilst pushing the thumb grip away, until a click is heard?** | | |
| | **Does the patient hold the inhaler with mouthpiece towards himself?** | | |
| | **Does the patient slide lever away until it clicks?** | | |
| | **Does the patient hold the inhaler in a horizontal position?** | | |
| | **Does the patient breath out slowly and then put inhaler in front of mouth?** | | |
| | **Does the patient place mouthpiece between lips and breathe in as deeply as possible?** | | |
| | **Does the patient remove inhaler from mouth and hold breath for about 10 seconds?** | | |
| | **After 10 seconds does the patient breathe out slowly?** | | |
| | **Does the patient close the inhaler by sliding thumb grip back towards him as far as it will go until it clicks?** | | |
| | **Does the patient gargle throat after use?** | | |

## Appendix 10: INCA SUN Statistical Analysis Plan (SAP)

## List of Abbreviations

| | |
|---|---|
| INCA | **IN**haler **C**ompliance **A**ssessment |
| ACT | Asthma Control Test |
| AQLQ | Asthma Quality of Life Questionnaire |
| BMI | Body Mass Index |
| EQ-5D-3L | European Quality of Life, 5 dimensions, 3 layers |
| FeNO | Fractional Exhaled Nitric Oxide |
| GINA | Global Initiative for Asthma |
| ITT | Intention To Treat |
| PP | Per protocol |
| PEFR | Peak Expiratory Flow Rate |
| QoL | Quality of Life |
| WPAI-Asthma | Work Productivity and Activity Impairment – Asthma Questionnaire |

## 1. INTRODUCTION

This is a prospective, randomised, controlled, multicentre, parallel study of patients with symptomatic asthma comparing two different educational interventions in Ireland. One arm will use electronic recorded and integrated information from the INCA$^{TM}$ device, peak expiratory flow rate (PEFR) and environmental data. In the second, current best practice comprising of adherence optimisation using inhaler proficiency score check list, asthma education, written action plans and inhaler training will be performed. The study is in two phases; an education and inhaler adherence optimisation followed by a medication adjustment phase.

## 2. OBJECTIVES

### 2.1 Primary objective

The study has two primary objectives:

1. To assess if a clinician's knowledge of objectively measured adherence and PEFR influences medication prescription step up therapy (such as monoclonal antibody). In other words, to see if adherence is incorporated into guideline directed clinical

decision making. This will be assessed by comparing the proportion of patients with 'inappropriate' asthma medication prescriptions in the control versus the active group and assessing the overall cost of these medication prescriptions at the end of the study.

2. To assess if giving feedback to the patient on their adherence using the INCA$^{TM}$ device and aligning this information to electronically recorded PEFR data, leads to a higher rate of long-term adherence, assessed over the last 12 weeks of the study, compared to usual care.

**2.2 Secondary objectives**

The secondary objectives are listed below. For each of the objectives, unless otherwise stated, the differences (proportions, means etc.) between the active and control group will be calculated and compared for two time periods - the first 8 weeks and additionally the last 12 weeks of the study.

***Economic objectives***

1. A cost-effectiveness and cost-utility analysis of the INCA educational intervention compared to the control arm will be performed. In addition, an economic evaluation of a national implementation of the INCA-SUN program will be conducted (budget impact analysis).
2. To compare the average time lost to work between the active and control groups

***Patient reported objectives***

1. To compare the Asthma Control Test (ACT), Asthma Quality of Life Questionnaire (AQLQ) scores, EQ-5D-3L scores, Work Productivity and Activity Impairment-Asthma (WPAI-Asthma) scores and PEFR rates between the active and control groups

***Clinical objectives***

2. To examine and compare the proportion of patients reaching stated clinical goals.
3. To compare the proportion of patients who are refractory, defined as having actual adherence ≥80%, ≥1 exacerbations, PEFR am/pm <80% and ACT ≤19.
4. To compare the proportion of patients who are non-adherent and remain uncontrolled, i.e. Actual Adherence <80%, PEFR am/pm <80% and ACT≤19.

5. To compare the time to first exacerbation (defined by ≥20% fall in PEFR and at least doubling of reliever use for 3 consecutive days or prescribed rescue oral steroid) between the active and control groups.
6. To compare the proportion of patients with inhaler related side effects including oral candidiasis between the active and control groups.
7. To compare changes in blood eosinophil's, periostin and Fractional Exhaled Nitric Oxide (FeNO) between the active and control groups.
8. To investigate the relationship of biomarker changes in relation to adherence.
9. To compare the proportion of patients who were clinically stabile (i.e. proportion of patients who required no daily reliever use in the month prior to study end) between the active and control groups.
10. To investigate the relationship between changes in FeNO (characterised into FeNO≥45ppb or FeNO<45ppb) and adherence.
11. To investigate the relationship between 7-day FeNO suppression and clinical and biomarker outcomes.

## 3. DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on the two primary outcomes. A sample of at least 112 patients per treatment group (a total of 224) is required.

Proportion of patients who received 'inappropriate' asthma medication prescriptions

Based on the INCA-1,(1) results, we anticipate that the difference in the proportion of patients who had step up therapy in the active group will be 10% versus 30% in the control group (a difference of 20%). We estimate that a sample size of 164 (82 per group) will provide a power of 90% at a significance level of 0.05 and accounting for a 10% drop out rate to detect a difference of 20% between the groups.

Mean adherence over the last 12 weeks of the study

For the second primary outcome, based on INCA-1 study,(1) we anticipate that the baseline (visit 1-2) mean adherence will be 0.65 with a standard deviation of 0.20. We also anticipate a mean {standard deviation (SD)} change from baseline to end of therapy in the INCA group of 0.15 (0.02) and in the control group of 0.05 (0.03), a 0.10 difference. Hence, using a two-

sided alpha of 0.05, we estimate that 112 patients per treatment group (total: 224) will provide 80% power to detect a treatment difference of 0.10, assuming a combined SD of 0.25 and a 10% drop out rate.

On the basis of these calculations, we aim to recruit at 112 patients in each group, giving a total of 224 patients.

Sample size calculations were also conducted for the secondary outcomes and can be seen in Appendix A.

## 4. RANDOMISATION AND BLINDING

Random allocation will take place at the end of the 7-day monitoring period, where patients will be randomised in an allocation ratio of 1:1 to receive recorded and integrated information from the INCA device, PEFR and environmental data or current best practice.

Patients will be stratified by site and day 7 FeNO (FeNO ≥45ppb or FeNO <45ppb). Allocation will be blocked using random permuted blocks of varying size of 2, 4 and 6. The randomisation schedule has been developed by a statistician and an independent clinical informatics manager using a computer generated randomisation programme. The clinical informatics manager will set up a password controlled Excel file containing the randomisation schedule for each individual site. The researcher will enter the patient/subject ID number and FeNO in the Excel file and the arm of the trial to which the patient is assigned will be revealed.

To avoid the risk of contamination between the active and the control group, the researchers delivering the education (best practise) to the control group patients will not have access to the control patients INCA$^{TM}$ device data. That is, the researcher will have limited access to INCA$^{TM}$ device data in that they will only have access to the INCA$^{TM}$ device data for active group and not the control group. The data outcome assessors will also be blinded to study subject treatment allocation.

## 5. ANALYSES SETS / POPULATIONS / SUBGROUPS

The primary analysis will be conducted on the intention to treat (ITT) basis. Secondary, per-protocol analyses will also be performed. ITT analyses will include all patients randomised to

the trial regardless of whether they have taken the study drug or not. A per-protocol analysis includes patients who comply in the most part (>80%) with the trial protocol.

# 6. ENDPOINTS / OUTCOME MEASURES

## 6.1 Primary Outcome Measures

1. Mean rate of adherence over the last 12 weeks of the study calculated from the INCA$^{TM}$ device,(2-4).
2. Proportion of necessary step up therapy prescriptions, calculated by looking at the INCA$^{TM}$ device data and determining whether the step-up therapy was necessary.

## 6.2 Secondary Outcome Measures

***Economic outcomes***

1. A cost-effectiveness and cost-utility analysis of the INCA educational intervention compared to the control arm will be performed. In addition, an economic evaluation of a national implementation of the INCA-SUN program will be conducted (budget impact analysis).
2. To compare the average time lost to work between the active and control groups.

***Patient reported outcomes***

1. To compare the Asthma Control Test (ACT), Asthma Quality of Life Questionnaire (AQLQ) scores, EQ-5D-3L scores, Work Productivity and Activity Impairment-Asthma (WPAI-Asthma) scores and PEFR rates between the active and control groups.

***Clinical outcomes***

2. To examine and compare the proportion of patients reaching stated clinical goals.
3. To compare the proportion of patients who are refractory, defined as having actual adherence ≥80%, ≥1 exacerbations, PEFR am/pm <80% and ACT ≤19.
4. To compare the proportion of patients who are non-adherent and remain uncontrolled, i.e. Actual Adherence <80%, PEFR am/pm <80% and ACT≤19.
5. To compare the time to first exacerbation (defined by ≥20% fall in PEFR and at least doubling of reliever use for 3 consecutive days or prescribed rescue oral steroid) between the active and control groups.

6. To compare the proportion of patients with inhaler related side effects including oral candidiasis between the active and control groups.
7. To compare changes in blood eosinophil's, periostin and Fractional Exhaled Nitric Oxide (FeNO) between the active and control groups.
8. To investigate the relationship of biomarker changes in relation to adherence.
9. To compare the proportion of patients who were clinically stabile (i.e. proportion of patients who required no daily reliever use in the month prior to study end) between the active and control groups.
10. To investigate the relationship between changes in FeNO (characterised into FeNo>45ppb Or FeNO<45ppb) and adherence.
11. To investigate the relationship between 7-day FeNO suppression and clinical and biomarker outcomes.

## 7. DATA COLLECTION

An electronic case record form will be used to collect all data. In addition to the outcome measures specified above, demographic and baseline information will be collected: age, gender, Body Mass Index (BMI), number of concomitant medicines, smoking history, baseline lung function and previous salmeterol/fluticasone Diskus$^{TM}$ use.

## 8. HANDLING OF MISSING DATA VALUES

Initially, if a patient has a missing value at the end of a visit, the last observation will be carried forward and used as the visit value. Furthermore, missing values will be imputed, if possible, using a suitable imputation method.

## 9. DESCRIPTION OF STATISTICAL METHODS

Data analysis and reporting will proceed according to CONSORT guidelines for randomised controlled trials,(5).

### 9.1 Demographic and Baseline Characteristics

In the first stage of the analysis, descriptive statistics will be used to describe recruited individuals and to investigate comparability of the trial arms at baseline.

The number of patients and percentage will be presented for categorical variables. For continuous variables that are normally distributed, the mean and standard deviation (SD) will be presented, while median and inter-quartile range will be presented for continuous variables that are not normally distributed.

### 9.2 Primary Endpoints

There are two co-primary endpoints, one relating to the promotion of adherence and the second to knowledge of adherence effects medication choices by clinicians.

1. To compare the proportion of patients between control and active group prescribed 'inappropriate' medication (appropriate refers to GINA suggested medication changes) at the end of the study, a logistic regression model adjusted for stratification variables, with results presented as odds ratios, 95% confidence intervals and *p*-values, will be used. Furthermore, the estimated costs associated with these prescriptions will be investigated.
2. To compare actual adherence (which incorporates the time of use, the interval between the doses and the technique of use), reported previously,(2-4) over the last 12 weeks of the study between the two groups, the primary analysis will be conducted on an ITT basis and adjusted for stratification variables {site and fractional exhaled nitric oxide (FeNO) suppression}. A linear regression model, with results presented as difference in means, 95% confidence intervals and *p*-values, will be used. Further adjustment will be made for any variables displaying marked imbalance between the arms at baseline.

### 9.3 Secondary Endpoints

#### *9.3.1. Economic and Cost-Effectiveness Analysis*

Economic analysis

An economic evaluation of national implementation of the INCA-SUN program will be provided. Data on the cost of the intervention (device, time taken to deliver, cost of training and salary cost of the trainer), medication costs, quality of life, exacerbations and other healthcare utilization and associated costs, such as unscheduled health care visits as well as

work productivity losses will be collected alongside the 32-week study. The outcome measures will be the incremental cost per exacerbation prevented and incremental cost per Quality Adjusted Life-Year (QALY). See Appendix C for more information on the economic evaluation.

Cost-effectiveness analysis

A cost-effectiveness and cost-utility analysis of the intervention compared to the control arm will be performed. Incremental cost-effectiveness ratios (ICERs) will be calculated from the data, to estimate how much additional cost is required for an additional unit of benefit. Uncertainty around this estimate will be indicated with 95% confidence intervals. A discount rate of 5% will be applied to all costs and QALYs occurring after the first year, in line with HIQA recommendations. The discount rate will be varied in univariate sensitivity analysis (with HIQA recommended rates of 0% and 6%).

### *9.3.2 Other Secondary Objectives*

For the remaining secondary objectives (see Section 2.2) the main analyses will involve intention-to-treat comparisons between the two groups, with transformation as appropriate after examination of distributions and adjustment for stratification variables. All analyses will use appropriate (that is, logistic or linear) regression models, with results presented as point estimates (odds ratios or difference in means), 95% confidence intervals and *p*-values. Further adjustment will be made for any variables displaying marked imbalance between the arms at baseline. All final models will undergo appropriate diagnostic testing to identify points of high influence or leverage, the adequacy of model fit and compliance with model assumptions.

For time to first exacerbation (defined by 20% or more fall in PEFR and at least doubling of reliever use for 3 consecutive days or prescribed rescue oral steroid) a log rank test and Cox's proportional hazards regression will be used, stratified for site and FeNO (as used in the randomisation procedure). Hazard ratios with 95% confidence interval and *p*-values will be presented.

## 9.4 Subgroup Analysis

A requirement of this study is that patients use a salmeterol/fluticasone inhaler. Some patients will have been using one previously and for others it will be new. Hence, a subgroup analysis

will be conducted by investigating only patients who have previously used a salmeterol/fluticasone inhaler and following this looking at those who never previously used a salmeterol/fluticasone inhaler.

## 10. SENSITIVITY ANALYSES

No current sensitivity analysis planned.

## 11. RATIONALE FOR ANY DEVIATION FROM PRE-SPECIFIED STATISTICAL ANALYSIS PLANS.

No current deviations from previous statistical plans.

## 12. QUALITY CHECK PLANS

Some of the quality checks will include:

- Ensuring any change to population criteria is documented.
- Checking suggested handling of data problems is appropriate.
- Checking individual inclusion / exclusion criteria correspond to the protocol deviation listings.
- Where there is uncertainty as to whether a patient will be included in the statistical analyses, this patient will be identified and referred to the trial monitoring committee for clarification.
- Checking appropriateness and completeness of the proposed statistical methods and presentation of results are in agreement with the protocol.
- Ensuring justification of any changes to planned analyses from those described in the protocol.
- Checking agreement of the details of any report with the objectives of the study.
- Checking the content of the report is appropriate and complete.

*Appendix A – Additional Sample Size Calculations*

**Sample size for AQLQ difference:** One hundred and sixty patients per treatment group provides an estimated 80% power to detect a clinically meaningful treatment difference of 0.5 for the secondary end point (change from baseline in AQLQ score over 12 weeks) by using a two-sided t-test and assuming an SD of 1.5 and a 10% dropout rate.

**Sample size for ACT difference:** Seventy-four patients per treatment group provides an estimated 90% power to detect a minimal clinical important difference of 3 points(6), by using a two-sided t-test and assuming an SD of 5.3 and a dropout rate of 10%.

**Sample size for cost:** Assuming a cost of Severe Refractory asthma of €4,000 (SD 2000) per annum, and for others €2000 (SD 2000) and estimating to see a cost difference between active and control of €1000 per annum an estimated sample size of 80 in each group is required.

**Sample size for PEFR AUC difference:** Eighty-two patients per treatment group provides an estimated 80% power to detect a treatment difference of 8% in PEFR by using a two-sided t test, assuming a SD of 17.3 and dropout rate of 10%.

***Appendix B –*** *Effectiveness evaluation*

Number of exacerbations and time to first exacerbation will be compared. An exacerbation will be as defined as an increase in symptoms; cough, sputum production and breathlessness within two weeks, in combination with a drop in PEFR of ≥20%. Moderate to severe asthma exacerbations (defined by prescribed rescue oral steroid, or admission to hospital, or emergency department attendance or general practitioner (GP) visitation with an asthma exacerbation) will be compared between the groups over the study period. Mild asthma exacerbations, {defined as the rate of salbutamol reliever use associated with a PEFR of 60% to 80% (predicted of personal best), when not associated with a moderate or severe exacerbation} over the 32-week study period will be compared among the active and control groups salbutamol use.

Spirometry lung function values, collected at each study visit will be compared between the two study groups. Quality of life (QoL), as assessed by the AQLQ and EQ-5D-3L derived utility will be compared among the study groups over the 32 week study period. The WPAI-asthma scores will be compared among the two groups.

**Longitudinal disease modelling.**

Employing multi-level survival analysis on the course of asthma over time we can assess the interaction of predictors including adherence, FeNO, blood biomarkers (peripheral blood eosinophils, periostin), symptoms and lung function and events (dependents) such as exacerbations in a continuous time domain.

***Appendix C – Economic evaluation***

Type of evaluation

Cost-utility analysis with quality adjusted life years gained (QALYs) as effectiveness outcome (to allow for across disease comparisons) supplemented by a secondary cost-effectiveness analysis with all treated exacerbations as effectiveness outcome (to allow for asthma specific comparisons).

Perspective

The proposed economic evaluation will adopt an Irish publicly-funded health perspective (including all substantial direct medical costs incurred in the treatment of the participants as recommended by the Irish Health Information and Quality Authority (HIQA) as well as a societal perspective (also including indirect costs such as work productivity losses).

Time horizon

A 32 week time horizon will be used, corresponding to the trial length. However, we anticipate that the time horizon is limited since it is less than one year and hence the impact of seasonal influences will not be assessed. As such, costs and effects may be impacted beyond the 32- week time horizon. Therefore in addition, economic modelling, based on an established asthma Markov model, may be used to assess the cost-effectiveness over a 10 year time horizon,(7).

Comparator

The INCA device intervention will be compared to routine care as described in this protocol.

Target population

Severe uncontrolled asthma patients as specified in this protocol.

Resource-use measurement, valuation and costs

The main areas of resource use to be collected are: (i) health care utilisation, (ii) medication costs and (iii) costs associated with the INCA intervention. Health care utilisation data will be collected on (i) numbers of GP visits, (ii) number and duration of Emergency department attendance and (iii) number, duration and reason for hospital admissions (if any). Medication costs will be collected including details of dose, frequency and type of medications use and

the duration of medication use. Information on concomitant medications will also be recorded, but information on costs, unless directly related, will not be included. The time for delivering the intervention and device cost will be recorded as part of the study protocol. The differential costs associated with managing patients in the two arms of the trial will be estimated from data from the trial and from unit costs available from the participating hospitals. GP visits cost between approximately €50 and €70 per visit,(8). Days in hospital will be costed using average cost per patient per day based on Drug Related Group (DRG) case-mix costs. These costs include all resources used during the hospital stay. Drug costs will be available via the Monthly Index of Medical Specialities (MIMS) or costs for reimbursable items under the community drug schemes. Time for delivering the intervention will be costed using the Health Sector Executive (HSE) salary scales at the time of the study, including pay related social insurance (PRSI).

Sensitivity analyses

Probabilistic (to assess parameter uncertainty) and deterministic (to assess key parameters that impact the ICER most) sensitivity analyses will be performed to assess the robustness of the ICER obtained via the model. Results of the deterministic analyses will be depicted using a tornado diagram. Scatter plots and cost-effectiveness acceptability curves (CEACs) will be used for the results of the PSA.

Budget impact analysis

To inform the payer regarding the affordability, a budget impact analysis will be presented along with the economic evaluation.

Outcomes

Asthma specific and general quality of life will be assessed using the AQLQ and EQ-5D-3L respectively. Utility will be derived from the EQ-5D scores using Irish valuation tariffs. It is anticipated that Irish valuation tariffs will be available by the end of the trial. In the absence of Irish public preference data, UK tariffs will be considered. Regarding the exacerbation outcome measure, statistical modelling will be used to assess the risk of exacerbations based on factors, including adherence rates, lung function and patient identified risks during the intervention, bearing in mind the duration of the interview.

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